General

Guideline Title

Management of cytomegalovirus infection in haemopoietic stem cell transplantation.

Bibliographic Source(s)

Emery V, Zuckerman M, Jackson G, Aitken C, Osman H, Pagliuca A, Potter M, Peggs K, Clark A, British Committee for Standards in Haematology, British Society of Blood and Marrow Transplantation, UK Virology Network. Management of cytomegalovirus infection in haemopoietic stem cell transplantation. Br J Haematol. 2013 Jul;162(1):25-39. [146 references] PubMed

Guideline Status

This is the current release of the guideline.

Recommendations

Major Recommendations

Definitions for the quality of the evidence (A–C) and strength of recommendations (strong [grade 1], weak [grade 2]) are given at the end of the "Major Recommendations" field.

Background

- Cytomegalovirus (CMV) infection and CMV disease should be diagnosed according to established, internationally accepted, standardized criteria (Grade 1C).
- Risk-adapted patient assessment should inform clinical management (Grade 1B).

Impact of Host and Donor CMV Serostatus

- All potential haemopoietic stem cell transplantation (HSCT) recipients should be tested for the presence of CMV immunoglobulin G (IgG) antibody at diagnosis (Grade 1C).
- Once optimum human leucocyte antigen (HLA) matching has been performed, a CMV IgG-negative donor should be chosen for a CMV IgG-negative recipient and a CMV IgG-positive donor should be chosen for CMV IgG-positive recipient when possible (Grade 1A).
- Donors or recipients who are initially found to be CMV IgG-negative should be retested pre-transplant to exclude primary CMV infection (Grade 1C).
- Apparent CMV seroconversion in potential allograft recipients who have received unscreened blood products should be actively investigated to exclude passively acquired antibody (Grade 1C).
- Any CMV IgG-negative HSCT recipient transplanted from a CMV IgG-negative donor who develops CMV infection post-transplant must

be reported to the Serious Hazards of Transfusion (SHOT) (Grade 1C).

Primary and Secondary Prophylaxis for CMV

- Primary prophylaxis with ganciclovir is not generally recommended as toxicity outweighs efficacy in HSCT patients (Grade 1B).
- Primary prophylaxis with aciclovir or valaciclovir can be deployed but only in conjunction with appropriate monitoring of CMV in the blood (Grade 1B).
- Valaciclovir or valganciclovir are valid treatment options for secondary prophylaxis with appropriate monitoring of CMV in the blood (Grade 1C).
- Intravenous immunoglobulins are not recommended for prophylaxis of CMV infection (Grade 1A).

Pre-emptive Therapy

- Real-time quantitative polymerase chain reaction (PCR) is the preferred option for monitoring CMV deoxyribonucleic acid (DNA) levels in HSCT patients (Grade 1B).
- All diagnostic laboratories should deploy the CMV international standard to allow CMV DNA loads to be compared between centres (Grade 1C).
- Monitoring of CMV DNA load should be undertaken at least weekly for the first 3 months post-HSCT (Grade 2C).
- CMV viral load monitoring should continue to 6–12 months if the patient has chronic graft-versus-host disease (GvHD) or prolonged T-cell immunodeficiency (Grade 1B).

Treatment Thresholds

Each transplant centre should have a risk-adapted policy detailing threshold values for treatment of CMV infection, taking into account patient factors and local PCR methodology (Grade 2C).

Antiviral Agents Used in Pre-emptive Therapy

- Ganciclovir is recommended as first line pre-emptive therapy for CMV in HSCT patients (Grade 1A).
- Oral valganciclovir is a useful alternative when gastrointestinal absorption is normal or minimally impaired (Grade 1B).
- Foscarnet is recommended as an alternative first line agent if neutropenia is present or for ganciclovir treatment failures (Grade 1A).
- Pre-emptive therapy with cidofovir can be considered as third line in patients unresponsive or intolerant of a ganciclovir preparation or foscarnet (Grade 2B).

Switching Pre-emptive Therapy

In patients where CMV DNA loads in blood increase by 1 $\log_{10}$ over 2 weeks of pre-emptive therapy with a first line drug, an alternative agent and drug resistance profiling should be considered (Grade 2C).

Antiviral Drug Resistance

- Drug resistance should be considered if the CMV DNA load in blood fails to respond after 14 days of therapy, especially in non-lymphopenic or multiply pre-treated patients (Grade 2C).
- Sequence analysis of the UL97 and UL54 genes is the preferred option for monitoring resistance to currently available drugs (Grade 1B).

Management of CMV Disease

- A multidisciplinary approach to management of CMV disease is required (Grade 1C).
- *De novo* CMV disease should be treated with ganciclovir or foscarnet, plus intravenous immunoglobulin (Grade 1B).
- CMV disease that develops while on pre-emptive therapy or is clinically progressive requires drug resistance testing, increased drug doses and/or a change of drug (Grade 1B).
- Reduction in immunosuppression, especially corticosteroid dosage, is strongly recommended (Grade 1B).

Definitions:

Quality of Evidence

The quality of evidence is graded as high (A), moderate (B) or low (C). To put this in context it is useful to consider the uncertainty of knowledge and whether further research could change what is known or is certain.

(A) High Further research is very unlikely to change confidence in the estimate of effect. Current evidence derived from randomised clinical trials without important limitations.

(B) Moderate Further research may well have an important impact on confidence in the estimate of effect and may change the estimate. Current evidence derived from randomised clinical trials with important limitations (e.g., inconsistent results, imprecision – wide confidence intervals or methodological flaws – e.g., lack of blinding, large losses to follow up, failure to adhere to intention to treat analysis), or very strong evidence from observational studies or case series (e.g., large or very large and consistent estimates of the magnitude of a treatment effect or demonstration of a dose-response gradient).

(C) Low Further research is likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate. Current evidence from observational studies, case series, or just opinion.

Strength of Recommendations

Strong (grade 1): Strong recommendations (grade 1) are made when there is confidence that the benefits do or do not outweigh harm and burden. Grade 1 recommendations can be applied uniformly to most patients. Regard as 'recommend'.

Weak (grade 2): Where the magnitude of benefit or not is less certain a weaker grade 2 recommendation is made. Grade 2 recommendations require judicious application to individual patients. Regard as 'suggest'.

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Cytomegalovirus infection in haemopoietic stem cell transplantation

Note: The guidelines also are relevant to other areas of haematological oncology where there is an increased risk of cytomegalovirus infection, such as haematological cancers where intense anti-T-cell therapy has been deployed.

Guideline Category

Diagnosis

Management

Prevention

Treatment

Clinical Specialty

Hematology

Infectious Diseases

Internal Medicine

Medical Genetics

Oncology

Intended Users

Advanced Practice Nurses

Physician Assistants

Physicians

Guideline Objective(s)

To expand and adapt previous guidance on management of cytomegalovirus infection in haemopoietic stem cell transplantation

Target Population

Patients with cytomegalovirus infection in haemopoietic stem cell transplantation

Interventions and Practices Considered

Assessment/Diagnosis

1. Diagnosis according to established, internationally accepted criteria
2. Risk-adapted patient assessment
3. Testing for the presence of cytomegalovirus (CMV) immunoglobulin G (IgG) antibody
4. Investigation of CMV seroconversion
5. Optimum human leucocyte antigen (HLA) matching for donors

Prevention/Management/Treatment

1. Ganciclovir
2. Aciclovir
3. Valaciclovir
4. Valganciclovir
5. Intravenous immunoglobulin
6. Real-time quantitative polymerase chain reaction (PCR)
7. CMV viral load monitoring
8. Foscarnet
9. Sequence analysis of the UL97 and UL54 genes for drug resistance screening
10. Reduction in immunosuppression

Major Outcomes Considered

- Signs and symptoms of cytomegalovirus (CMV) infection
- Risk factors of CMV infection (e.g., measured by incidence of transfusion-transmitted CMV infection, incidence of CMV reactivation, incidence of CMV-related complications, survival/mortality)
- Effectiveness of CMV prevention (e.g., measured by CMV infection, CMV reactivation)
- Sensitivity and accuracy of diagnostic tests
- Efficacy/effectiveness of treatments (e.g., measured by response rates, resistance rates, progression to CMV, survival)
- Treatment-related toxicity

Methodology

Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

The production of these guidelines involved literature review to 1 May 2012 including Medline, PubMed, and Cochrane reviews databases.

Number of Source Documents

Not stated

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Quality of Evidence

The quality of evidence is graded as high (A), moderate (B) or low (C). To put this in context it is useful to consider the uncertainty of knowledge and whether further research could change what is known or is certain.

(A) High Further research is very unlikely to change confidence in the estimate of effect. Current evidence derived from randomised clinical trials without important limitations.

(B) Moderate Further research may well have an important impact on confidence in the estimate of effect and may change the estimate. Current evidence derived from randomised clinical trials with important limitations (e.g., inconsistent results, imprecision – wide confidence intervals or methodological flaws – e.g., lack of blinding, large losses to follow up, failure to adhere to intention to treat analysis), or very strong evidence from observational studies or case series (e.g., large or very large and consistent estimates of the magnitude of a treatment effect or demonstration of a dose-response gradient).

(C) Low Further research is likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate. Current evidence from observational studies, case series, or just opinion.

Methods Used to Analyze the Evidence

Review of Published Meta-Analyses

Systematic Review

Description of the Methods Used to Analyze the Evidence

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) nomenclature was used to evaluate levels of evidence (see the "Rating Scheme for the Strength of the Evidence" field).

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

The production of these guidelines involved the following steps:

- Establishment of a working group comprising experts in the field of allogeneic transplantation and clinical virology.
- Development of key recommendations based on randomized, controlled trial evidence. Due to the paucity of randomized studies, some recommendations are based on literature review and a consensus of expert opinion.
- The Grading of Recommendations Assessment, Development and Evaluation (GRADE) nomenclature was used to assess the strength of recommendations (see the "Rating Scheme for the Strength of the Recommendations" field).

Rating Scheme for the Strength of the Recommendations

Strength of Recommendations

Strong (grade 1): Strong recommendations (grade 1) are made when there is confidence that the benefits do or do not outweigh harm and burden. Grade 1 recommendations can be applied uniformly to most patients. Regard as 'recommend'.

Weak (grade 2): Where the magnitude of benefit or not is less certain a weaker grade 2 recommendation is made. Grade 2 recommendations require judicious application to individual patients. Regard as 'suggest'.

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

External Peer Review

Internal Peer Review

Description of Method of Guideline Validation

The production of these guidelines involved the following steps:

- Initial review of manuscript, performed by the UK Clinical virology Network, British Society of Blood and Marrow Transplantation executive committee, and the British Committee for Standards in Haematology (BCSH) Haem-Onc Task Force.
- Final review by sounding boards of the British Society for Haematology and British Society of Blood and Marrow Transplantation.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for each recommendation (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Appropriate prevention and management of cytomegalovirus infection in haemopoietic stem cell transplantation

Potential Harms

Drugs Used for Cytomegalovirus (CMV) Prevention

- Ganciclovir prophylaxis significantly reduced the incidence of CMV infection and disease during the period of prophylaxis. However neutropenia occurred in up to 30% of cases treated and infective complications were increased.
- Prolonged exposure of CMV to ganciclovir, especially in the setting of T-cell depletion, may encourage resistance, as occurs in solid organ transplantation.
- Routine use of aciclovir or valaciclovir for CMV prophylaxis is relatively non-toxic but will result in some patients being overtreated.

Side Effects of Drugs Used to Treat CMV Infection

- Ganciclovir: myelosuppression
- Valganciclovir: haemolysis, nausea/vomiting, fever, rash, mental state changes, urinary symptoms
- Foscarnet: electrolyte abnormalities, renal impairment, nausea/vomiting, genitourinary, urinary symptoms
- Cidofovir: renal impairment, nausea/vomiting, ocular
- In 1 study (which compared 60 mg/kg foscarnet with ganciclovir 5 mg/kg), renal insufficiency was more common with foscarnet and myelosuppression with ganciclovir.

Qualifying Statements

Qualifying Statements

These evidence-based guidelines expand and adapt previous guidance. While specifically focusing on allogeneic haemopoietic stem cell transplantation (HSCT), they are relevant to other areas of haematological oncology where there is an increased risk of cytomegalovirus (CMV) infection, such as haematological cancers where intense anti-T-cell therapy has been deployed.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Staying Healthy

IOM Domain

Effectiveness

Patient-centeredness

Safety

Identifying Information and Availability

Bibliographic Source(s)

Emery V, Zuckerman M, Jackson G, Aitken C, Osman H, Pagliuca A, Potter M, Peggs K, Clark A, British Committee for Standards in Haematology, British Society of Blood and Marrow Transplantation, UK Virology Network. Management of cytomegalovirus infection in haemopoietic stem cell transplantation. Br J Haematol. 2013 Jul;162(1):25-39. [146 references] PubMed

Adaptation

These evidence-based guidelines expand and adapt previous guidance:

- Tomblyn M, Chiller T, Einsele H, Gress R, Sepkowitz K, Storek J, Wingard JR, Young JA & Boeckh MJ. Guidelines for preventing infectious complications among hematopoietic cell transplantation recipients: a global perspective. Biology of Blood and Marrow Transplantation. 2009;15:1143–1238.
- Andrews PA, Emery VC & Newstead C. Summary of the British transplantation society guidelines for the prevention and management of CMV disease after solid organ transplantation. Transplantation. 2011;92:1181–1187.

Date Released

2013 Jul

Guideline Developer(s)

British Committee for Standards in Haematology - Professional Association

Source(s) of Funding

British Committee for Standards in Haematology

Guideline Committee

British Committee for Standards in Haematology

Composition of Group That Authored the Guideline

Authors: Vincent Emery, Department of Virology, University College London School of Life and Medical Sciences, London; Mark Zuckerman, Department of Virology, King's College Hospital, London; Graham Jackson, Department of Haematology, Freeman Road Hospital, Newcastle; Celia Aitken, West of Scotland specialist virology centre, Gartnavel General Hospital, Glasgow; Husam Osman, Birmingham HPA Laboratory, Birmingham Heartlands Hospital, Birmingham; Anthony Pagliuca, Department of Haematology, King's College Hospital, London; Mike Potter, Section of Haemato-oncology, The Royal Marsden NHS Foundation Trust, London; Karl Peggs, Department of Haematology, University College London Hospitals, London; Andrew Clark, Blood and Marrow Transplant Unit, Beatson Oncology Centre, Glasgow, UK

Financial Disclosures/Conflicts of Interest

The authors report no conflicts of interest.

Guideline Status

This is the current release of the guideline.

Guideline Availability

Electronic copies: Available from the British Journal of Haematology Web site .

Print copies: Available from the British Committee for Standards in Haematology; Email: bcsh@b-s-h.org.uk.

Availability of Companion Documents

None available

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI Institute on October 18, 2013.

Copyright Statement

Disclaimer

NGC Disclaimer